



Heated water-based exercise training reduces 24-hour ambulatory blood pressure levels in resistant hypertensive patients: A randomized controlled trial (HEX trial) ☆,☆☆,★



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ABSTRACT

Background: Regular exercise is an effective intervention to decrease blood pressure (BP) in hypertension, but no data are available concerning the effects of heated water-based exercise (HEX). This study examines the effects of HEX on BP in resistant hypertensive patients.

Methods: This is a parallel, randomized controlled trial. 125 nonconsecutive sedentary patients with resistant hypertension from a hypertension outpatient clinic in a university hospital were screened; 32 patients fulfilled the study requirements. The training was performed for 60-minute sessions in a heated pool (32 °C), three times a week for 12 weeks. The HEX protocol consisted of callisthenic exercises and walking inside the pool. The control group was asked to maintain habitual activities. The main outcome measure was change in mean 24-hour ambulatory BP (ABPM).

Results: 32 patients (HEX n = 16; control n = 16) were randomized; none were lost to follow-up. Office BPs decreased significantly after heated water exercise (36/12 mm Hg). HEX decreased 24-hour systolic (from 137 ± 23 to 120 ± 12 mm Hg, p = 0.001) and diastolic BPs (from 81 ± 13 to 72 ± 10 mm Hg, p = 0.009); daytime systolic (from 141 ± 24 to 120 ± 13 mm Hg, p < 0.0001) and diastolic BPs (from 84 ± 14 to 73 ± 11 mm Hg, p = 0.003); and nighttime systolic (from 129 ± 22 to 114 ± 12 mm Hg, p = 0.006) and diastolic BPs (from 74 ± 11 to 66 ± 10 mm Hg, p < 0.0001). The control group after 12 weeks significantly increased in 24-hour systolic and diastolic BPs, and daytime and nighttime diastolic BPs.

Conclusion: HEX reduced office BPs and 24-hour ABPM levels in resistant hypertensive patients. These effects suggest that HEX may be a potential new therapeutic approach in these patients.

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1. Introduction

Systemic hypertension is a highly prevalent disease, affecting almost 20% of the population worldwide [1]. Patients who do not achieve target

blood pressure (BP) despite the use of, at least, three classes of antihypertensive drugs to keep BP controlled are considered resistant to treatment [1]. Resistant hypertension (RH) is prevalent in 10 to 30% of all hypertensive patients, and these patients are more likely to develop adverse cardiovascular events [2,3]. Thus, the control of BP in resistant hypertension is a recognized clinical challenge.

Regular physical exercise reduces systemic blood pressure (BP) and is broadly recommended by current hypertension guidelines [4,5]. A recent study showed that conventional exercise has positive effects on BP in patients with resistant hypertension [6]. However, the search for feasible, acceptable, effective, and safe exercise modalities to control BP in patients with uncontrolled hypertension continues [7–9].

Studies have documented seasonal variations in BP, with higher values in winter and lower values in warm seasons [10–11]. One study showed that exercise and sauna have discreet effects on BP in patients with untreated hypertension [12]. Although the evidence of heat as a treatment for hypertension is weak, one study of heated water-based exercise training has previously demonstrated a decrease in office

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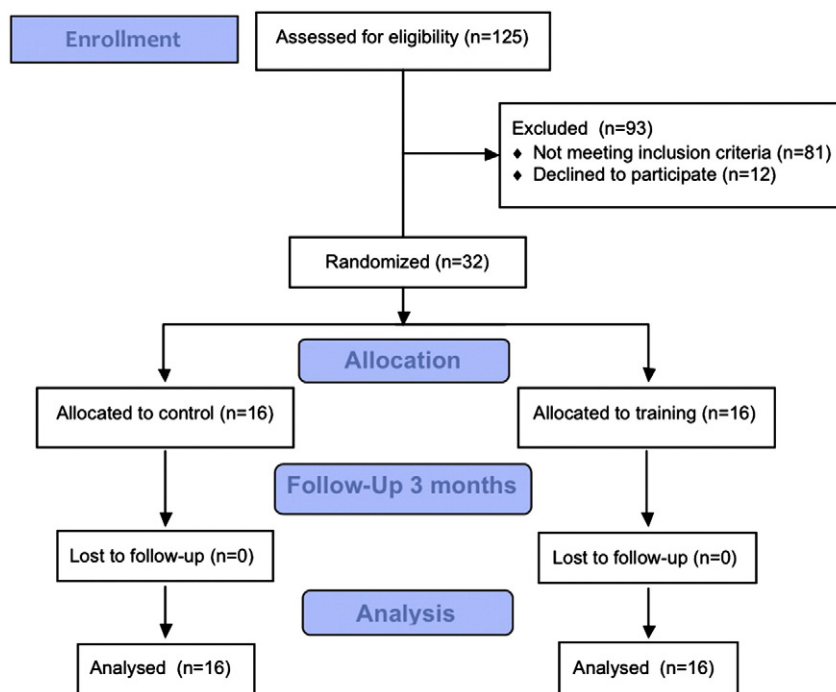


Fig. 1. Study design.

systolic blood pressure in patients with essential hypertension [13]. Nonetheless, other studies about heated water-based exercise and BP are quite inconsistent [14,15]. In different populations, this strategy seems to have beneficial effects on renal function, oxygen uptake, endothelial function, sympathetic activity, and cardiovascular function [14–19], but they were attributed mainly to water immersion.

Our objective was to evaluate the effects of heated water-based exercise training on BP in resistant hypertensive patients.

2. Methods

2.1. Population

All patients were referred from the hypertension outpatient clinic at the University Hospital of the University of São Paulo in May 2011. We selected nonconsecutive patients between 40 and 65 years of age with RH for more than 5 years, who in the previous 6 months had unchanged or regular use of three antihypertensive drugs, with an office systolic BP of at least ≥ 140 mm Hg, and diastolic BP ≥ 90 mm Hg. We used medical records to exclude patients with a history of secondary hypertension, evidence of target organ damage (i.e., heart, eye, kidney, and brain), or coronary artery disease. We also excluded those patients with any chronic illness that could limit their capacity to exercise, were smokers, or were participating in regular physical activity.

2.2. Study design

This was a randomized controlled, parallel group study conducted in a single center in Brazil. The patients were allocated to the intervention (HEX) versus control (non-HEX) group with a 1:1 randomization using a drawing of lots (envelops in a bag). All participants underwent a cardiopulmonary treadmill exercise test before and after the study. Ambulatory blood pressure monitoring (ABPM) was performed before and after the 12-week program. The patients were familiar with this procedure, as it is part of the routine clinical evaluation. All patients were instructed to maintain the same antihypertensive treatment during the entire study period. The local ethics committee approved all procedures. The volunteers read a detailed description of the protocol and provided written informed consent.

2.3. Cardiopulmonary exercise test

A cardiopulmonary exercise test was performed before the study to exclude patients with coronary artery disease and after the study to assess the training effect. All patients were asked to refrain from both strenuous physical activity on the morning of the test and to have a light breakfast, without any stimulants (coffee, tobacco, alcohol), no less

than 2 h before the start of the test. They underwent the test on a programmable treadmill (Series 2000, Marquette Electronics, Milwaukee, WI, USA) in a temperature-controlled room (21–23 °C) between 08:00 and 11:00 AM, with a standard 12-lead continuous ECG monitor (Max 1, Marquette Electronics). Blood pressure monitoring was obtained with the patient at rest, during effort, and during recovery. Minute ventilation, oxygen uptake, carbon dioxide output, and other cardiopulmonary variables were acquired breath-by-breath by a computerized system (Vmax 229 model, SensorMedics, Yorba Linda, CA, USA). The respiratory exchange ratios were recorded as the one minute averaged samples obtained during each stage of the Balke protocol [20]. A satisfactory test was characterized by a peak of respiratory exchange ratio ≥ 1.05 and symptoms of maximum effort. The highest VO_2 uptake level was considered the peak value (peak VO_2).

Table 1
Baseline characteristics of the resistant hypertensive patients.

	All patients (n = 32)	HEX (n = 16)	Control (n = 16)
Gender F/M	17/15	8/8	10/6
Age (years)	53.7 \pm 6.0	55.0 \pm 5.9	52.4 \pm 5.9
BMI (kg) m ²	29.6 \pm 4.7	29.2 \pm 4.9	30.1 \pm 4.5
Ethnicity W/B	10/22	6/10	4/12
SBP office (mmHg)	162.3 \pm 18.4	164.1 \pm 8.8	159.1 \pm 16.7
DBP office (mmHg)	89.4 \pm 9.4	88.8 \pm 9.5	90.1 \pm 9.2
N ^o antihypertensive drugs	4 (3–6)	4 (3–6)	4 (3–6)
Diuretic	100%	100%	100%
CCB	78%	75%	81%
ACE inhibitor	62%	62%	62%
ARB	31%	37%	25%
Beta-blocker	62%	62%	62%
Vasodilator	53%	56%	50%
Aldosterone antagonists	46%	50%	43%
Central inhibitor	31%	37%	25%
Hypoglycemic drug	28%	31%	25%
ASA	15%	25%	6%

HEX: heated water-base exercise training; F/M: female/male; BMI: body mass index; W/B: white/black; SBP and DBP: systolic blood pressure and diastolic blood pressure; CCB: calcium channel blocker; ACE inhibitor: angiotensin-converting-enzyme; ARB: angiotensin II receptor blocker; ASA: acetylsalicylic acid.

Table 2
Number of valid ambulatory blood pressure monitoring measurements pre- and post-intervention.

	HEX (n = 16)		Control (n = 16)	
	Pre	Post	Pre	Post
24 h	78.4 ± 7.9 (89%)	77.8 ± 6.9 (88%)	77.1 ± 7.4 (87%)	78.4 ± 8.3 (89%)
Daytime	57.4 ± 6.9 (89%)	57.3 ± 6.7 (89%)	58.3 ± 7.0 (91%)	58.0 ± 6.5 (90%)
Nighttime	21.1 ± 4.3 (87%)	20.8 ± 2.8 (86%)	18.5 ± 4.1 (76%)	20.9 ± 4.1 (87%)

Mean ± SD (%) of the expected measurements.

2.4. Blood pressure measurements

Blood pressure measurement in the office was done according to recommended guidelines [21]. After a 5-minute rest period, BP was measured three times with patients in the seating position using the auscultatory method (mercury sphygmomanometer, Heidji, São Paulo, Brazil) taken at intervals of 1 min, in the same arm at the same time of day for each participant pre- and post-intervention, between 9 AM and 2 PM, by a staff professional who was blinded to the study data. The BP value used was the mean of the 3 readings.

ABPM was started before patients began the program and 72 h after the last session in the heated pool. Both measurements began at the same time of the day (between 01:00 and 02:00 PM) using a Spacelabs model 90207 ABP monitor (Spacelabs Medical Inc., Redmond, WA). The BP cuff was worn on the non-dominant arm with the proper cuff size. Subjects were instructed to perform their habitual daily activities, not to exercise, and to relax and straighten the arm during the recording interval for daytime ABPM. The ABPM was analyzed by an examiner who was blinded to the patient groups. ABPM

data were classified by mean, 24-hour, daytime, and nighttime periods for systolic and diastolic BPs, separately. The daytime and nighttime periods were based on the time patients got out of and into bed, respectively. The monitor was programmed to measure BP every 15 min during the daytime and every 20 min during nighttime periods. ABP data were accepted with >75% of the measurements successfully taken. BP load was defined as the percentages of BP measurements that were ≥130/80 mm Hg in the 24-hour period, 135/85 mm Hg during the daytime period, and 120/70 mm Hg during the nighttime period. Individual BP measurements were reviewed for missing and erroneous values.

2.5. Exercise training protocol

The exercise sessions took place in the afternoon (1:30 to 2:30 PM) and were performed in a controlled temperature (30–32 °C) swimming pool. Patients were immersed in warm water up to the xiphoid process, and the sessions were performed three times a

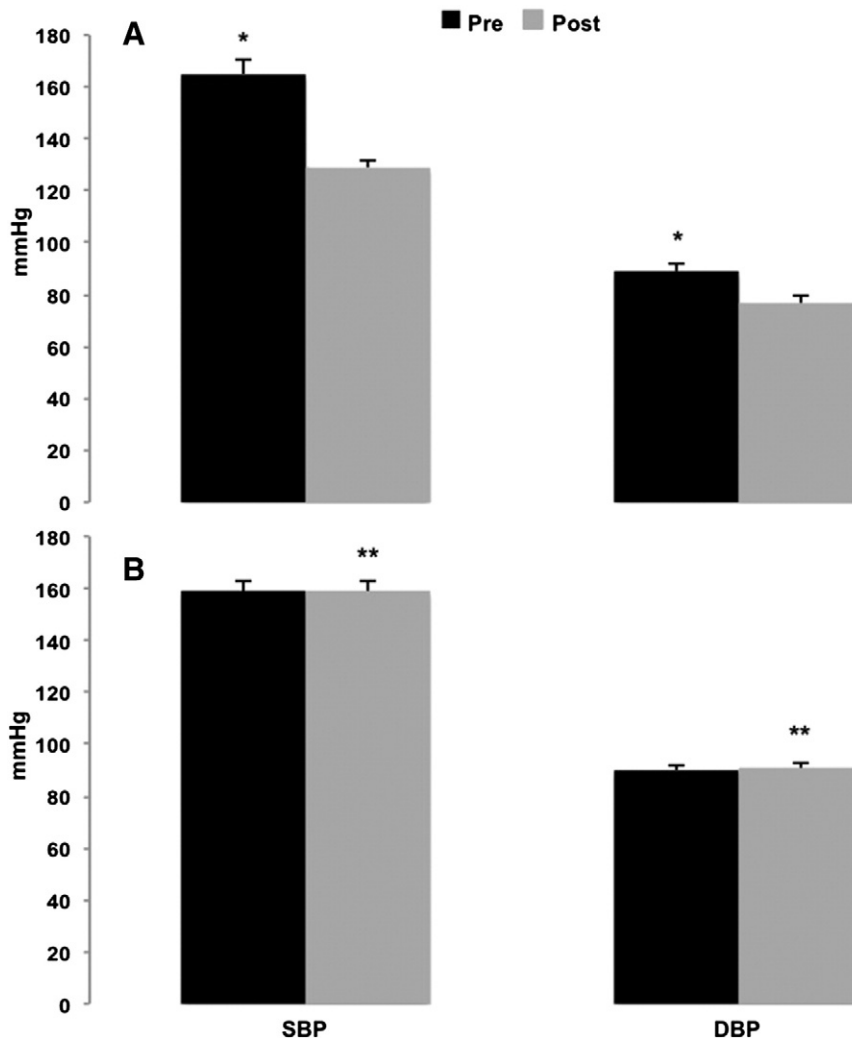


Fig. 2. Office blood pressure at baseline and after 12 weeks: A, exercise training in heated water immersion and B, control group; *: within-group differences ($p < 0.05$) and **: between-group differences ($p < 0.05$). Data are presented as mean ± standard error.

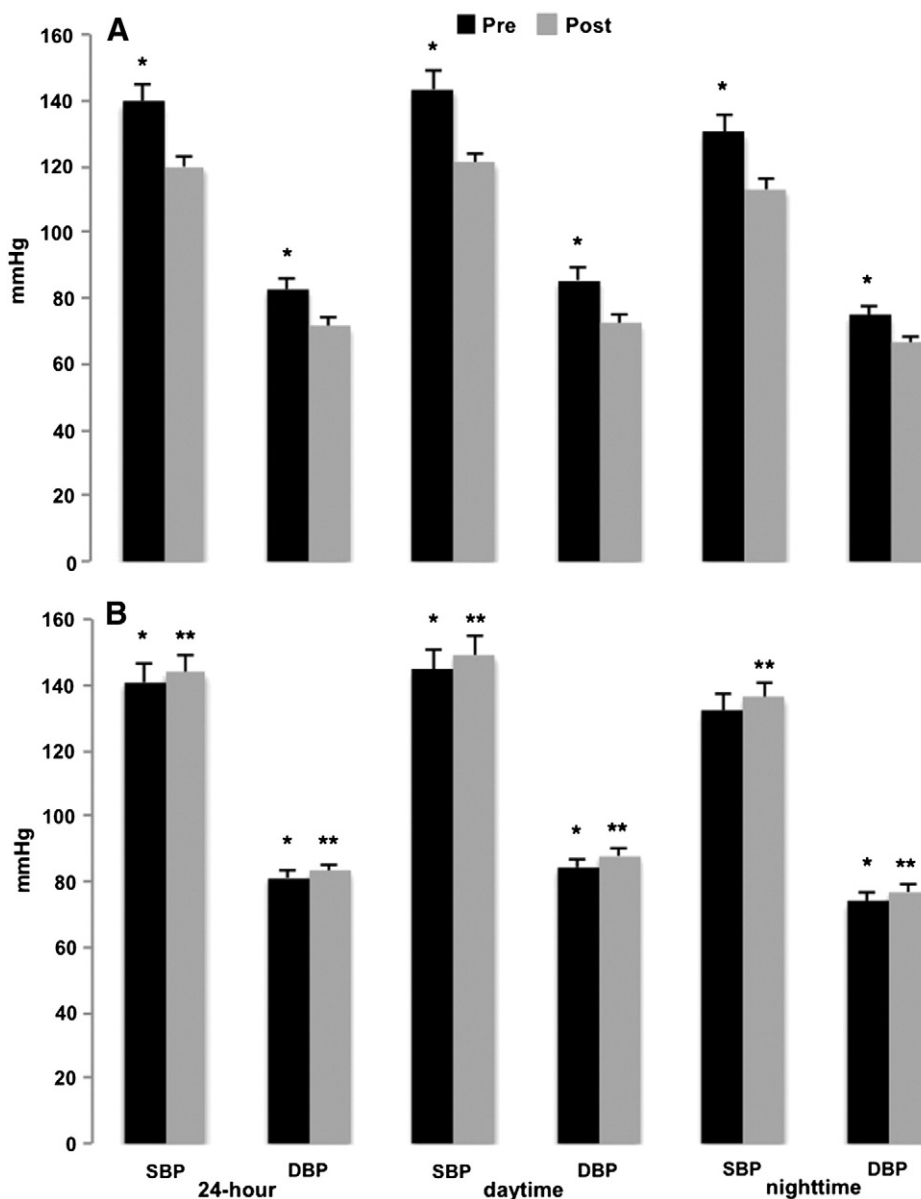


Fig. 3. Average of 24-hour period, daytime and nighttime ABPMs at baseline and after 12 weeks: A, exercise training in heated water immersion and B, control group; *: within-group differences ($p < 0.05$) and **: between-group differences ($p < 0.05$). Data are presented as mean \pm standard error.

week, for 12 weeks. All subjects were instructed not to add any leisure-time exercise during the study period. All patients were either unused to or had no previous experience with swimming. The exercise sessions consisted of 60 min: 5 min of warming up, 20 min of callisthenic exercises against water resistance (upper and lower limbs), 30 min of walking inside the pool at a pace that was between “relatively easy and slightly tiring” (between 11 and 13 on the Borg Scale), and 5 min of cooling down and stretching [22]. The control group was advised to maintain daily activities without exercise training during the 12-week period.

2.6. Statistical analysis

Descriptive statistics were used to describe the characteristics of the subjects. Data are presented as mean \pm standard deviation. The Shapiro–Wilk test was applied to ensure a Gaussian distribution of the data. Unpaired t test was used to compare the baseline characteristics between training and control groups. Repeated measures analysis of variance (ANOVA) was performed with time (pre and post) and intervention (HEX and control) as repeated factors. Comparison between baseline and subsequent time points (within-group differences), as well as between intervention groups at each time point (between-group differences), were done in both 24-hour, awake and sleep averages, as well as hourly averages. Bonferroni post-hoc analysis was performed to identify significant differences that were indicated. The Mann–Whitney U test was also used for non-parametric analysis. The level of significance was set at p

< 0.05 . The statistical program SPSS 20.0 for Mac (SPSS Inc., Chicago IL, USA) was used to perform the statistical analyses.

3. Results

We assessed 125 patients during the enrollment period, 93 were excluded, and 32 patients were randomized to intervention or control group (Fig. 1). The women were predominantly postmenopausal and did not use hormone replacement therapy. Only one in the HEX group was premenopausal and did not use oral contraceptives. The two groups had similar age, body mass index, and preexisting antihypertensive medication use. Characteristics of the study population are given in Table 1.

Baseline office and ambulatory BPs did not differ between HEX training and control groups. All patients kept the same antihypertensive medication through the study. The protocol was well tolerated by all patients, and no adverse events occurred during the study. The adherence of the patients to HEX was 100% in all sessions. All ABPM data were of good quality and there was no significant difference between pre- and

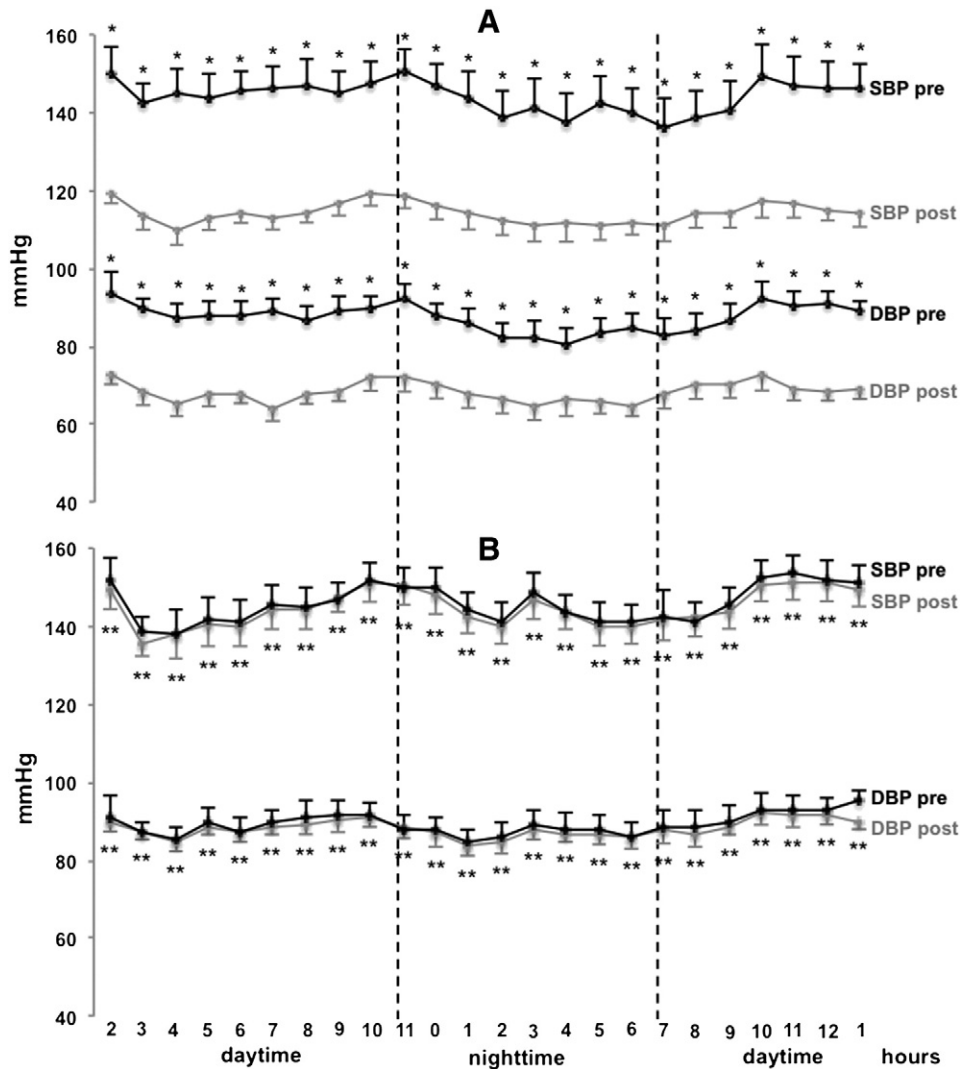


Fig. 4. Hourly averages of systolic and diastolic blood pressures during daytime and nighttime at baseline and after 12 weeks: A, exercise training in heated water immersion and B, control group; *: within-group differences ($p < 0.05$) and **: between-group differences ($p < 0.05$). Data are presented as mean \pm standard error.

post-intervention in both groups (Table 2). ABPM measurements began and ended at the same time of day in the Hex training and control groups ($1:25 \pm 0:15$ to $1:20 \pm 0:13$ PM and $1:30 \pm 0:10$ to $1:30 \pm 0:15$ PM, respectively).

Systolic and diastolic office BPs decreased significantly after exercise in heated water immersion by 36.5 ± 7.8 mm Hg ($p < 0.0001$) and 11.9 ± 1.9 mm Hg ($p = 0.004$), respectively, but did not change in the control group after follow-up (Fig. 2).

HEX significantly decreased systolic and diastolic ABPM, respectively, in the 24-hour period (19.5 ± 11.0 and 11.1 ± 3.1 mm Hg), daytime (22.3 ± 12.6 and 13.0 ± 3.6 mm Hg) and nighttime (17.4 ± 9.1 and 8.5 ± 2.1 mm Hg) (Fig. 3A). In the control group, there was a significant increase in systolic and diastolic BPs, respectively (24-hour: 3.0 ± 0.1 and 2.1 ± 1.2 mm Hg; daytime: 4.4 ± 2.2 and 3.5 ± 2.1 mm Hg and nighttime diastolic 3.1 ± 1.9 mm Hg) (Fig. 3B). Fig. 4A and B shows systolic and diastolic curves during 24-hour ABPM at baseline and after 12 weeks in both groups, respectively. HEX significantly lowered the hourly average systolic and diastolic BPs in the study group, but BP did not change in the control group.

The exercise program led to a significant decrease in systolic and diastolic BP loads in 24-hour, daytime and nighttime periods, but BPs during these time periods did not change in the control group after 12 weeks (Fig. 5A and B, respectively).

The hemodynamic and ventilatory measurements during a cardiopulmonary exercise test pre- and post-intervention are displayed in Table 3. The two groups had similar baseline values of systolic and diastolic BPs, heart rate, peak oxygen consumption (peak VO_2) and respiratory exchange rate (RER). After 12 weeks, HEX significantly increased peak VO_2 and RER, and decreased systolic BP at rest and maximum.

4. Discussion

To the best of our knowledge, this is an original study demonstrating the positive effects of heated water-based exercise training in patients with resistant hypertension in a randomized controlled trial. The main finding of this study is that heated water-based exercise leads to a significant reduction on 24-hour, daytime, and nighttime blood pressures in these patients. The risk of events correlates more closely to ABPM than to office BP [23], mainly with nighttime period ABPM measurements [24,25]. The improvement in the peak VO_2 only in the HEX group indicates that they trained at an adequate intensity level and that the intervention was really composed by exercise plus immersion in heated water.

The beneficial effects of land-based exercise on ABPM were demonstrated in previous studies [26]. To our knowledge, only one evaluated

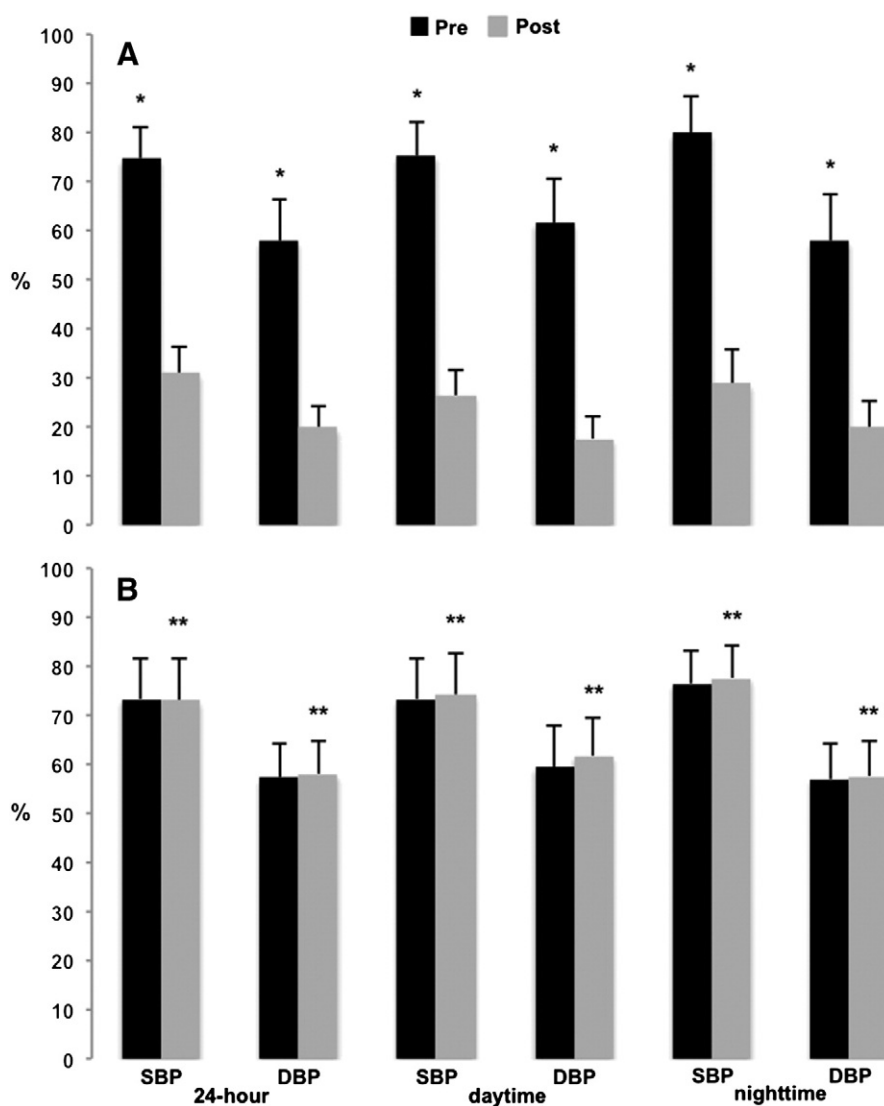


Fig. 5. Blood pressure load for 24-hour period, daytime and nighttime ABPMs at baseline and after 12 weeks: A, exercise training in heated water immersion and B, control group; *: within-group differences ($p < 0.05$) and **: between-group differences ($p < 0.05$). Data are presented as mean \pm standard error.

its effects in resistant hypertensive patients [6]. In brief, the authors found that land-based exercise reduces systolic and diastolic daytime ABPMs by 6/3 mm Hg, respectively, after an interval training program 3 times weekly for 8 to 12 weeks. Although the results between

populations of different studies are not comparable, our results show a more pronounced reduction in BP, suggesting that the heated water immersion among 30 to 32 °C temperature may have an additional effect in these patients. Contrary to this hypothesis, it has been demonstrated

Table 3

Hemodynamic and ventilatory variables during cardiopulmonary exercise test pre- and post-intervention.

	HEX (n = 16)		Control (n = 16)	
	Pre	Post	Pre	Post
Heart rate (bpm)				
Rest	68.1 \pm 18.3	64.5 \pm 15.2	70.3 \pm 14.9	72.0 \pm 12.9
Peak	143.4 \pm 22.2	145.0 \pm 23.6	136 \pm 26.3	135.7 \pm 26.1
Systolic BP (mm Hg)				
Rest	160.2 \pm 26.5	136.4 \pm 14.6 ^a	157.6 \pm 18.1	157.8 \pm 17.7 ^b
Peak	198.3 \pm 33.3	175.1 \pm 28.0 ^a	193.6 \pm 17.8	194.0 \pm 17.8 ^b
Diastolic BP (mm Hg)				
Rest	82.8 \pm 15.4	76.7 \pm 14.4	86.3 \pm 10.5	87.1 \pm 8.2
Peak	93.2 \pm 17.4	86.8 \pm 23.0	100.9 \pm 18.8	101.5 \pm 18.2
Peak VO ₂ (ml kg min)	25.0 \pm 4.6	27.9 \pm 4.0 ^a	22.1 \pm 4.6	20.6 \pm 4.1 ^b
RER	1.1 \pm 0.05	1.2 \pm 0.09 ^a	1.1 \pm 0.04	1.1 \pm 0.06 ^b

BP, blood pressure; peak VO₂, peak oxygen consumption; RER, respiratory exchange ratio.

^a Within-group differences ($p < 0.05$).

^b Between-group differences ($p < 0.05$).

that the acute effects on BP is similar for land-based and water-based exercise [27]. However, these individuals performed the exercise in water with a 27 °C temperature and they did not have resistant hypertension. Randomized clinical trials comparing these two strategies, land-based and water-based exercises in different temperatures, should be done to evaluate this hypothesis.

Whether water temperature has a significant influence on hypotensive effect is only speculation. Few studies have analyzed the effects of heat on blood pressure in hypertensive patients [13–15]. For example, acute aerobic exercise followed by sauna bathing in subjects with untreated hypertension had positive effects on 24-hour systolic BP [12]. Nonetheless, the benefit that we found in our study does not seem to be the result of acute effects from heat or exercise, as the ABPM were done 72 h after the last session. A previous study also demonstrated that the post-exercise hypotension effect occurred ≥ 24 -hour but ≤ 48 h after the last training session [28]. Additionally, blood pressure increases to pre-training levels only 1 week after a training program cessation [29].

There is one study that showed that heated water-based exercise reduced office systolic BP in patients with essential hypertension who did not receive anti-hypertensive therapy [13]. However, this intervention was not isolated, as it was associated with the recommendation to reduce weight, to limit salt consumption, and to stop smoking and drinking alcohol [13].

Our findings indicate that HEx is an effective antihypertensive therapy in patients that are not responsive to drug therapy. Multiple mechanisms could support this theory, but they are speculative. Exercise training has been shown to decrease sympathetic and increase vagal nerve activity, and improve sensitivity of the baroreceptor reflex after exercise training [28]. Additional effects on the cardiovascular system attributed to heated water immersion could be arterial vasodilatation and a reduction in volemia [17,18]. A decrease in the concentration of renin, angiotensin II, aldosterone, a reduction in renal sympathetic outflow and an increase in nitric oxide and atrial natriuretic peptide release have been previously demonstrated in healthy subjects and in patients with heart failure [17,18,21,22]. On the other hand, changes in neurohormonal secretion, peripheral resistance reduction, and diuresis increase, reported as a result of heated water-based exercise in healthy subjects and heart failure patients, were not associated with a BP decrease [21,22,29]. Exercise training has also been shown to improve numerous health-related parameters including endothelial function [30], arterial stiffness [7], insulin sensitivity [31], fasting insulin [31], markers of sympathetic activity [30], and central body fat [31]. Based on these studies, decreased total peripheral resistance appears to be the primary mechanism by which blood pressure is reduced after HEx. Thus, increased muscular blood flow followed by a reduction in peripheral vascular resistance, and a reduction in the vasoconstrictor system are among the suggested mechanisms. A previous study demonstrated that two weeks of sauna treatment improved impaired endothelial function in patients with coronary risk factors, and this was accompanied by a significant reduction in BP [32]. It is possible that this benefit is associated with higher **endothelial nitric oxide synthase (eNOS)** activity and up-regulation of eNOS gene expression by increasing shear stress.

4.1. Study limitation

As in many studies like this one, it is not possible to eliminate the Hawthorne and placebo effect of the supervised training in these results. In order to try to reduce these possible confounders, control group participants were also observed and encouraged to continue their antihypertensive treatment as prescribed. In fact, even with monitoring of drug adherence, it is very difficult to separate the effect on BP due to the HEx from that of higher adherence to medication. No matter what the causes were of the beneficial effects on BP, the impact on cardiovascular risk factors are positive and promising for the treatment of RH.

Some patients may have had normal values of ABPM in our study and therefore they could not be considered as having truly resistant hypertension. However, we included patients with resistant hypertension as defined by previous statements (office BP $\geq 140/90$ mm Hg and requirement ≥ 3 classes of medications/day) [1]. On the other hand, the outcomes were evaluated by ABPM, as we considered it more appropriate to blind the investigator to this analysis.

4.2. Clinical implications

Resistant hypertension is a multifactorial disease including physical inactivity, nonadherence, secondary hypertension, increased vascular stiffness, sympathetic tone, and neurohormonal secretion [1–3].

Lifestyle and pharmacological management are not sufficient to control BP in resistant hypertensive patients. Recently, invasive procedures like renal sympathetic denervation or carotid baroreceptor stimulation have represented new frontiers in the treatment of this condition [33]. Along with this, our findings demonstrate a new potent, non-invasive and cheaper procedure that significantly reduces systolic and diastolic BPs in this population. The beneficial effects on BP that were observed in true and white-coat hypertension have important clinical consequences, because both conditions are associated with higher cardiovascular risk [27]. It has been estimated that 5.0/2.0 mm Hg reductions in systolic and diastolic BPs, respectively, result in a 6% to 14% reduction in cardiovascular events [34].

4.3. Perspectives

This study reinforces the value of exercise training associated with antihypertensive therapy in hypertensive patients. Heated water-based exercise induced beneficial effects on BP in patients with resistant hypertension, and there were no signs of adverse reactions. In fact, heated water-based exercise training tended to normalize the levels of BP in patients with resistant hypertension.

Studies comparing exercise training in heated water with that on land will be needed to better understand the mechanisms of the BP lowering in resistant hypertension. Research involving a large number of patients, long-term training, and pool water at different temperatures would be required in the future.

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